REMARKS

I. Status of the Claims

Claims 21, 23 and 24 have been cancelled without waiver, prejudice or disclaimer. New claims 27-31 have been added. Support for the new claims can be found in the claims as originally filed and on page 22, lines 19-26 of the Specification. Claims 1, 19, 20, 22 and 26 have been amended to correct typographical errors and properly format claims and claim language. Support for the amendments to the claims can be found in the claims as originally filed and throughout the specification, including the exemplified compounds.

The specification has been amended to reflect the corrections made to the claims. In addition, the definition of "heterocycloalkyl" and "heteroaryl" have been amended. The groups deleted from "heterocycloalkyl" were properly placed in the definition of "heteroaryl" except for "methylenedioxyl" which was deleted since it is neither a "heterocycloalkyl" and "heteroaryl" moiety.

No new matter has been added by the present amendment.

Upon entry of this amendment, claims 1-20, 22 and 25-31 will be pending.

II. Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-26 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants address each of the Examiner's rejections under § 112, second paragraph in turn.

1. "Claim 1 is indefinite as the definition of R^5 is unclear. Note in line 20 of claim 1, R^5 is recited as $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl but again in line 23 it recites the same groups. It is not clear what is the difference between these two definitions of R^5. The definition of R^5 is therefore ambiguous."

This rejection has been rendered moot by the amendment of claim 1 to remove the duplicate recitation of "(C_1-C_6)alkylamino, amino(C_1-C_6)alkyl". Applicants respectfully request this rejection be withdrawn.

2. "Recitation of the term "alkyl" in claim 1 is indefinite as specification on page 5 offers two distinct definitions of the same term. The term "alkyl" is defined on page 5, line 12-14 differs from that is recited in lines 22-27 which not only include cyclic alkyl with examples as several cycloalkyls but also halogen substituents. It is not clear what is difference between 'alkyl' and 'cycloalkyl' recited in the claims. Similarly, it is unclear what is 'haloalkyl' defined in claim 1 and the alkyl with halogen substituents recited in specification."

As would be understood by one of skill in the art and as defined in Applicants' specification, an "alkyl" group, refers to a saturated monovalent hydrocarbon radical having straight or branched moieties or combinations thereof. Specification, page 5, lines 12-14. Also as would be understood by one of skill in the art, a "cycloalkyl" group refers to a cyclic "alkyl" group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl). Thus, the term "alkyl" is meant to be distinct from the term "cycloalkyl". This distinction is made further evidence by the fact that R^4 can be either a "(C_1-C_6)alkyl" or a "(C_3-C_{10})cycloalkyl". Specification, page 2, line 3 and line 7.

Also as would be understood by one of skill in the art, the term "haloalkyl" refers to an "alkyl" group wherein at least one of the hydrogen is substituted by a "halo" or "halogen" moiety (e.g., trifluoromethyl, -CF_3), each as set forth on page 5 of Applicants' specification. Applicants believe that the Examiner has mistakenly included Applicants' definition of the term "halogen" in its reference to "cyclic alkyl and alkenyl" groups.

Applicants respectfully request this rejection be withdrawn.

3. "Claims 21, 22, 24 and 26 are indefinite as these claims recite the broad recitation "cancer", and the claims also recites "leukemia" which is the narrower statement of the range/limitation. Note this a double inclusion of single element leukemia in a broader limitation "cancer". See also Ex parte White 127 USPQ 261. In addition, these claims recite

"other autoimmune diseases" which is unclear as to what these "other autoimmune diseases" are. Specification has no definition of this term."

While neither agreeing or disagreeing with the Examiner's comments, this rejection has been rendered moot by the present amendment to the claims. Applicants respectfully request this rejection be withdrawn.

III. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 21-26 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one of skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in MPEP 2164.01:

> Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent are to make and use the claimed invention.... See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPOQ2d 1271, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.") A patent need not teach, and preferably omits, what is well known in the art.
>
> ...
>
> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation...The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

Here, Applicants' claimed invention is:

(i) a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from the group consisting of organ transplant rejection, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid

disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human;

(ii) a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human; and

(iii) a method for treating or preventing a disorder or condition selected from the group consisting of organ transplant rejection, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and autoimmune diseases in a mammal, including a human,

each based on the use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional agents which modulate a mammalian immune system or with an ant-iinflammatory agent, effective in treating the disorder or condition.

As the Examiner is aware, the specification must be enabling to one of skill in the art. MPEP 2164.05(b). Accordingly, one of skill in the art must be able to make and/or use Applicants' claimed pharmaceutical composition and claimed methods without undue experimentation in view of Applicants' specification.

Here, on page 20, line 27 through page 23, line 2 of the Specification, Applicants' claimed pharmaceutical composition and various modes of administration, including dosage ranges are described. In addition, on page 23, line 3 through page 24, line 25, assays to determine whether a compound of the invention is effective for use in Applicants' claimed composition or methods is described. Based on this description, one of skill in the art would understand how to make and/or us Applicants' claimed invention.

As set forth in MPEP 2164.06, citing *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) for support, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Here, as recited in the

claims, a compound of claim 1 or its pharmaceutically acceptable salt thereof for use in the claimed pharmaceutical compositions and methods must be effective in:

(a) treating or preventing a disorder or condition selected from the group consisting of organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and autoimmune diseases or

(b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3).

As set forth above, the Specification provides an *in vitro* assay test to determine:

> [t]he ability of the compounds of formula I or their pharmaceutically acceptable salts to inhibit Janus Kinase 3, and consequently, demonstrate their effectiveness for treating disorders or conditions characterized by Janus Kinase 3 .... Specification, page 23, lines 3-6.

Thus the specification provides the requisite guidance and direction as to which compound of formula I or its pharmaceutically acceptable salt is encompassed by the claimed pharmaceutical composition and methods. As to the amount of compound of formula I or its pharmaceutically acceptable salt encompassed by the claimed pharmaceutical composition and methods, one of skill in the art would understand that such an amount would need to be determined on a case by case basis and various factors would need to be considered including for example, the compound administered, the mode of administration, and the patient to be treated. Regardless, the specification provides requisite guidance and direction in the form of dosage ranges depending upon the mode of administration.

Still further, to the extent that a compound of formula I or its pharmaceutically acceptable salt acts as an "immunosuppressive agent for organ transplants" (Specification, page 1, lines 5-10), a compound of the invention can be said to "prevent" transplant rejection.

Thus, the Specification as written would enable one of skill in the art to make and/or use Applicants' claimed pharmaceutical composition and methods without undue experimentation. Applicants respectfully request this rejection be withdrawn.

IV. First Rejection Under 35 U.S.C. § 103

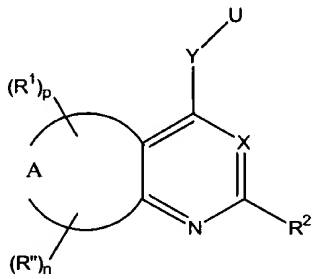
Claims 1-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cockerill et al., WO 98/02438 ("Cockerill").

Applicants contend that the present invention is not *prima facie* obvious in view of Cockerill. As the Examiner is well aware, the Board of Patent Appeals and Interferences has stated that "to establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention." *Ex Parte Levengood*, 28 U.S.P.Q. 2d 1300, 1301 (BOPAI 1993). Not only must there be evidence of motivation, but also, the skilled worker must have an expectation that the combination of teachings would be successful. As set forth in detail below, the Cockerill reference relied upon by the Examiner, taken alone or in any combination, fails to provide the requisite teaching, suggestion, incentive or inference to motivate one of ordinary skill in the art to modify the cited reference to arrive at Applicants' claimed invention.

It is the Examiner's position that the compounds described in Cockerill generically include Applicants' claimed compounds. It is also the Examiner's position that Cockerill "...teaches the equivalency of exemplified core and the substituents shown in examples 1-41 with those contemplated and claimed in the definition of various groups of formula I." The Examiner thus concludes that it would have been obvious to one having ordinary skill in the art at the time [...] the invention was made to make compounds with pyrrolopyrimidine core variously substituted in said ring as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in

view of the equivalency teaching outline above." Applicants respectfully disagree and traverse the rejection.

Cockerill describes bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors of the following formula (I):



where A represents:

> ...a fused 5, 6, or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or $S(O)_m$,..., the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrmidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or $S(O)_m$ atoms.

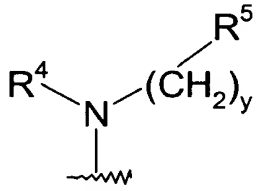
Cockerill, page 11, lines 11-17. On page 11, lines 29-31, Cockerill lists eighteen (18) possible "A" groups among which a pyrrole moiety is listed. On pages 16-17, Cockerill provides fifteen (15) various "A" groups among which various regioisomers of a pyrrolo moiety are provided.

However, as the Examiner is well aware, and as set forth in M.P.E.P. 2144.08, the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness (emphasis added). *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). In addition, "some motivation to select the claimed species or subgenus must be taught by the prior art (emphasis added)." *In re Duel*, 51 F.3d at 1558-9, 34 USPQ2d at 1215. Thus Cockerill must provide some

motivation to select Applicants' claimed subgenus and species of compounds containing a core pyrrolopyrimidine ring. Cockerill fails to do so.

Instead, as stated by the Examiner, Cockerill treats each of the "A" groups as equivalents. Based on this equivalency, Cockerill fails to provide the requisite guidance, teaching or suggestion as to how to pick and choose among the numerous "A" groups and select a pyrrolo moiety, much less the pyrrolo regioisomer fused to a pyrimidine moiety as in Applicants' claimed invention.

Cockerill still further fails to provide the requisite teaching or suggestion to pick and choose among the numerous variables of formula (I) and arrive at Applicants' claimed pyrrolopyrimidine compound containing the following moiety:



where R^5 is a substituted (C_3-C_9)heterocycloalkyl.

Cockerill fails to teach or suggest Applicants' claimed subgenus. Absent such teachings or suggestions, Cockerill would not render Applicants' claimed invention obvious. Applicants respectfully request this rejection be withdrawn.

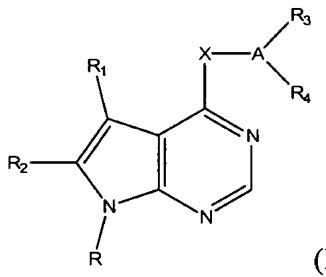
V. Second Rejection Under 35 U.S.C. § 103

Claims 1-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Buzzetti et al., EP 0 795 556 ("Buzzetti").

Applicants contend that the present invention is not *prima facie* obvious in view of Buzzetti. As the Examiner is well aware, the Board of Patent Appeals and Interferences has stated that "to establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention." *Ex Parte Levengood*,

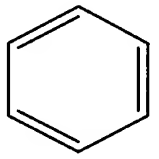
28 U.S.P.Q. 2d 1300, 1301 (BOPAI 1993). Not only must there be evidence of motivation, but also, the skilled worker must have an expectation that the combination of teachings would be successful. As set forth in detail below, the Buzzetti reference relied upon by the Examiner, taken alone or in any combination, fails to provide the requisite teaching, suggestion, incentive or inference to motivate one of ordinary skill in the art to modify the cited reference to arrive at Applicants' claimed invention.

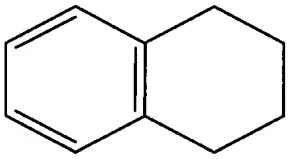
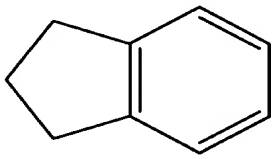
Buzzetti describes 4-substituted pyrrolopyrimidine compounds as tyrosine kinase inhibitors of formula (I):

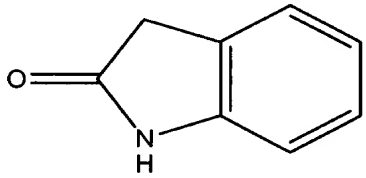


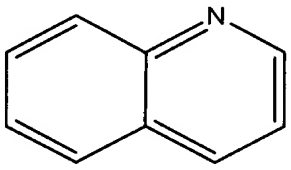
(I).

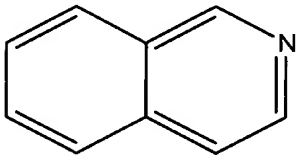
The "A" group of Buzzetti's compounds of formula (I) is defined as "a mono- or bicyclic chosen from phenyl, pyridine, tetralin, indan, 2-oxindole, quinoline, isoquinoline and indole." Thus, Buzzetti's "A" group is limited to the following structures:



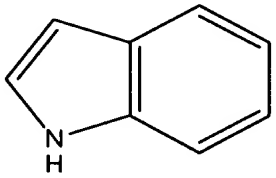
phenyl , pyridine ,  tetralin ,  indan ,



oxindole , 

quinoline , 

isoquinoline , and



indole .

In contrast, the "A" group of Applicants' claimed compounds is R^5. R^5 of Applicants' claimed invention is defined as a substituted (C_3-C_9)heterocycloalkyl. None of Buzzetti's "A" groups would constitute a (C_3-C_9)heterocycloalkyl group. Thus, Buzzetti does not teach or suggest Applicants' claimed compounds, much less their use in pharmaceutical compositions and methods of treatment. Applicants' claimed invention is not obvious in view of Buzzetti. Applicants respectfully request this rejection be withdrawn.

VI. Claim Objections

Claims 22, 24 and 26 are objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claims 21, 23 and 25. This rejection has been rendered moot by the present amendment. Applicants respectfully request this rejection be withdrawn.

VII. Double Patenting

Claims 1-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending application no. 09/956,645 (the '645 application). Applicants respectfully traverse this rejection.

As the Examiner is aware, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S. C. § 103 obviousness determination. As set forth above, a 35 U.S. C. § 103 obviousness determination requires a teaching or suggestion to modify the reference of rejection and arrive at Applicants' claimed invention with a reasonable expectation of success. Here, the '645 application fails to teach or suggest the claimed invention of Applicants' present application. R^5 of the present application and of the '645 application are completely distinct. R^5 of the present application is a substituted heterocycloalkyl group while R^5 of the '645 application is a moiety that does not contain a heteroatom. Furthermore, the '645 application fails to provide the requisite teaching or suggestion to modify its R^5 group to a heterocycloalkyl group as in the present application. Applicants' claimed invention is not obvious in view of the claims 1-12 of the '645 application. Applicants respectfully request this rejection be withdrawn.

VIII. Conclusion

Applicants respectfully request reconsideration of the subject application in view of the above remarks. The subject application is now in condition for allowance and early notice to that effect is respectfully solicited.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 16-1445. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

Date: October 21, 2002

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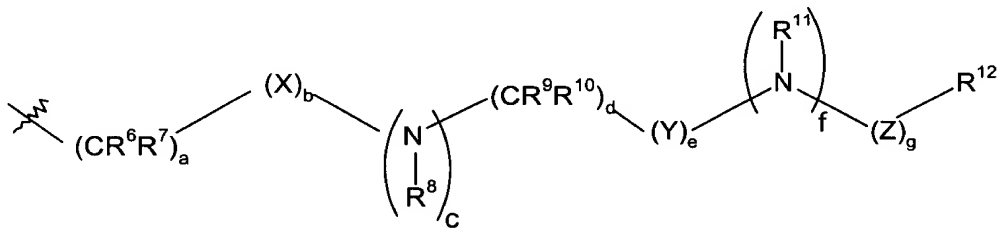
MARKED-UP VERSION OF THE SPECIFICATION

(1) Page 2, lines 3-24:

--R^4 is selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_2$-$C_6)$alkenyl, and $(C_2$-$C_6)$alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_6)$acyloxy, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, cyano, nitro, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl or $(C_1$-$C_6)$acylamino; or R^4 is $(C_3$-$C_{10})$cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1$-$C_6)$acyloxy, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, cyano, cyano$(C_1$-$C_6)$alkyl, trifluoromethyl$(C_1$-$C_6)$alkyl, nitro, nitro$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$acylamino;

R^5 is ~~$(C_2$-$C_9)$~~ $(C_3$-$C_9)$heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH, $(C_1$-$C_6)$alkylamino-CO-, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, nitro, cyano$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, nitro$(C_1$-$C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$acylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$acylamino, amino$(C_1$-$C_6)$acyl, amino$(C_1$-$C_6)$acyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$acyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$acyl, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-S$(O)_m$, $R^{15}R^{16}$NS$(O)_m$, $R^{15}R^{16}$NS$(O)_m$ $(C_1$-$C_6)$alkyl, R^{15}S$(O)_m$ R^{16}N, R^{15}S$(O)_m R^{16}$N$(C_1$-$C_6)$alkyl$_2$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1$-$C_6)$alkyl$_2$ or a group of the formula



II

wherein a is 0, 1, 2, 3 or 4;--

(2) Page 3, lines 7-25:

--Z is carbonyl, C(O)O-, ~~C(O)NR-~~ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen and ~~or~~ (C_1-C_6)alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)acylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, cyano, cyano(C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl or (C_1-C_6)acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, (C_1-C_6)acyl, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$ amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_1-C_6)alkylamino, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, amino(C_1-C_6)acyl(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-(C_1-C_6)alkyl, R^{15}C(O)NH, R^{15}OC(O)NH, R^{15}NHC(O)NH, (C_1-C_6)alkyl-$S(O)_m$, (C_1-C_6)alkyl-$S(O)_m$-(C_1-C_6)alkyl, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m$ (C_1-C_6)alkyl, $R^{15}S(O)_m$ R^{16}N, or $R^{15}S(O)_mR^{16}N(C_1$-$C_6)$alkyl, wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl;--

(3) Page 3, line 26 through Page 4, line 26:

--R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, ~~hydoxy~~ hydroxy, nitro, carboxy, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, and $(C_3$-$C_{10})$cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are optionally ~~substittued~~ substituted by one to three groups selected from halo, hydroxy, carboxy, amino $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, $(C_5$-$C_9)$heteroaryl, $(C_2$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$cycloalkyl or $(C_6$-$C_{10})$aryl; or R^2 and R^3 are each independently $(C_3$-$C_{10})$cycloalkyl, $(C_3$-$C_{10})$cycloalkoxy, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, $(C_6$-$C_{10})$arylamino, $(C_1$-$C_6)$alkylthio, $(C_6$-$C_{10})$arylthio, $(C_1$-$C_6)$alkylsulfinyl, $(C_6$-$C_{10})$arylsulfinyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_6$-$C_{10})$arylsulfonyl, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkoxy-CO-NH-, $(C_1$-$C_6)$alkyamino-CO-, $(C_5$-$C_9)$heteroaryl, $(C_2$-$C_9)$heterocycloalkyl or $(C_6$-$C_{10})$aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-CO-NH-, $(C_1$-$C_6)$alkoxy-CO-NH-, $(C_1$-$C_6)$alkyl-CO-NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH-$(C_1$-$C_6)$alkoxy, carboxy, carboxy$(C_1$-$C_6)$alkyl, carboxy$(C_1$-$C_6)$alkoxy, benzyloxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl, amino, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonylamino, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxycarbonylamino, $(C_1$-$C_6)$alkylamino, $((C_1$-$C_6)$alkyl$)_2$amino, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)$alkyl$)_2$amino$(C_1$-$C_6)$alkyl, hydroxy, $(C_1$-$C_6)$alkoxy, carboxy, carboxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-CO-NH-, $(C_1$-$C_6)$alkyl-CO-NH-, cyano, $(C_5$-$C_9)$heterocycloalkyl, amino-CO-NH-, $(C_1$-$C_6)$alkylamino-CO-NH-, $((C_1$-$C_6)$alkyl$)_2$amino-CO-NH-, $(C_6$-$C_{10})$arylamino-CO-NH-, $(C_5$-$C_9)$heteroarylamino-CO-NH-, $(C_1$-$C_6)$alkylamino-CO-NH-$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)$alkyl$)_2$amino-CO-NH-$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylamino-CO-NH-$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroarylamino-CO-NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfonyl, $(C_6$-$C_{10})$arylsulfonylamino, $(C_6$-$C_{10})$arylsulfonylamino$(C_1$-$C_6)$alkyl,

(C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_5-C_9)heteroaryl or (C_2-C_9)heterocycloalkyl.--

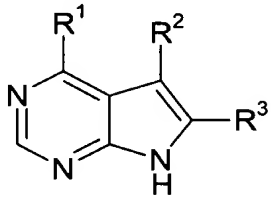
(4) Page 5, line 28 through page 6, line 14:

--~~(C_2-C_9)~~ (C_3-C_9)Heterocycloalkyl when used herein refers to pyrrolidinyl, tetrahydrofuranyl, ~~dihydrofuranyl,~~ tetrahydropyranyl, ~~pyranyl, thiopyranyl,~~ aziridinyl, oxiranyl, ~~methylenedioxyl, chromenyl,~~ isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, ~~1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl,~~ morpholinyl, ~~1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl,~~ piperazinyl, ~~chromanyl,~~ etc. One of ordinary skill in the art will understand that the connection of said (C_2-C_9)heterocycloalkyl rings is through a carbon or a sp^3 hybridized nitrogen heteroatom.

~~(C_2-C_9)~~ (C_3-C_9)Heteroaryl when used herein refers to furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzoxazinyl, dihydrofuranyl, pyranyl, thiopyranyl, chromenyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, chromanyl; etc. One of ordinary skill in the art will understand that the connection of said (C_2-C_9)heteroaryl ~~heterocycloalkyl~~ rings is through a carbon atom or a sp^3 hybridized nitrogen heteroatom.--

MARKED UP VERSION OF THE CLAIMS

1. (Amended) A compound of the formula



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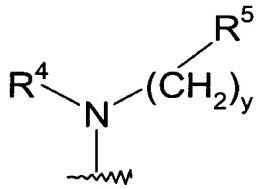
or the pharmaceutically acceptable salt thereof; wherein

R^1 is a group of the formula

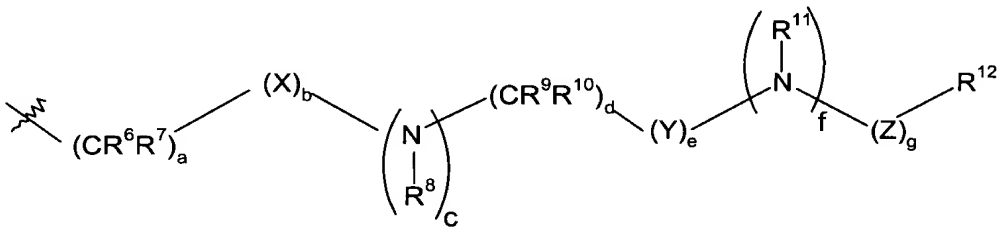


wherein y is 0, 1 or 2;

R^4 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_4)alkoxy, (C_1-C_6)acyloxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, cyano, nitro, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or (C_1-C_6)acylamino; or R^4 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)acylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, cyano, cyano(C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl or (C_1-C_6)acylamino;

R^5 is ~~(C_2-C_9)~~ (C_3-C_9)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, (C_1-C_6)acyl, (C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, ~~(C_1-C_6)alkylamino, amino(C_1-C_6)alkyl,~~ hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl,

trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, amino(C_1-C_6)acyl(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, $R^{15}R^{16}N$-CO-O-, $R^{15}R^{16}N$-CO-(C_1-C_6)alkyl, (C_1-C_6)alkyl-$S(O)_m$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m$ (C_1-C_6)alkyl, $R^{15}S(O)_m R^{16}N$, $R^{15}S(O)_m R^{16}N$(C_1-C_6)alkyl, wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl, or a group of the formula



II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or –C(=N-cyano)-;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, C(O)O-, ~~C(O)NR-~~ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen and ~~or~~ (C_1-C_6)alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)acylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, cyano, cyano(C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl or (C_1-C_6)acylamino;

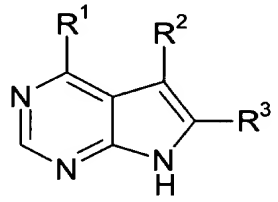
R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, (C_1-C_6)acyl, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$ amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_1-C_6)alkylamino, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-

C_6)alkyl, halo(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, amino(C_1-C_6)acyl(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, $R^{15}R^{16}N$-CO-O-, $R^{15}R^{16}N$-CO-(C_1-C_6)alkyl, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, (C_1-C_6)alkyl-$S(O)_m$, (C_1-C_6)alkyl-$S(O)_m$-(C_1-C_6)alkyl, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m$ (C_1-C_6)alkyl, $R^{15}S(O)_m$ $R^{16}N$, or $R^{15}S(O)_mR^{16}N$(C_1-C_6)alkyl, wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, ~~hydoxy~~ hydroxy, nitro, carboxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and (C_3-C_{10})cycloalkyl, wherein the alkyl, alkoxy or cycloalkyl groups are optionally ~~substituted~~ substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6)alkylthio, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_5-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl, (C_3-C_9)cycloalkyl or (C_6-C_{10})aryl; or R^2 and R^3 are each independently (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_6-C_{10})arylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)acyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyamino-CO-, (C_5-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl or (C_6-C_{10})aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-NH-, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy, carboxy, carboxy(C_1-C_6)alkyl, carboxy(C_1-C_6)alkoxy, benzyloxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_6-C_{10})aryl, amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonylamino, (C_6-C_{10})aryl(C_1-C_6)alkoxycarbonylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-, cyano, (C_5-C_9)heterocycloalkyl, amino-CO-NH-, (C_1-

C_6)alkylamino-CO-NH-, ((C_1-C_6)alkyl)$_2$amino-CO-NH-, (C_6-C_{10})arylamino-CO-NH-, (C_5-C_9)heteroarylamino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino-CO-NH-(C_1-C_6)alkyl, (C_6-C_{10})arylamino-CO-NH-(C_1-C_6)alkyl, (C_5-C_9)heteroarylamino-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonylamino, (C_6-C_{10})arylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_5-C_9)heteroaryl or (C_2-C_9)heterocycloalkyl.

19. (Amended) A compound ~~according to claim 1, wherein~~ of the formula



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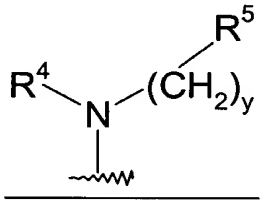
or the pharmaceutically acceptable salt thereof; wherein

R^1 is a group of the formula

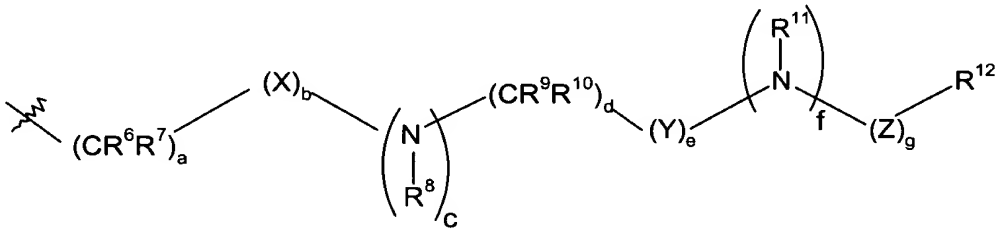


wherein y is 0, 1 or 2;

R^4 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_4)alkoxy, (C_1-C_6)acyloxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, cyano, nitro, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or (C_1-C_6)acylamino; or R^4 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)acylamino, (C_1-C_6)alkylamino, ((C_1-

C_6)alkyl)$_2$amino, cyano, cyano(C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl or (C_1-C_6)acylamino;

R^5 is (C_2-C_9)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, (C_1-C_6)acyl, (C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, amino(C_1-C_6)acyl(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-(C_1-C_6)alkyl, (C_1-C_6)alkyl-S(O)$_m$, $R^{15}R^{16}$NS(O)$_m$, $R^{15}R^{16}$NS(O)$_m$ (C_1-C_6)alkyl, R^{15}S(O)$_m$ R^{16}N, R^{15}S(O)$_m$$R^{16}$N($C_1$-$C_6$)alkyl, or a group of the formula



II

wherein

m is 0, 1 or 2;

R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl;

a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is S(O)$_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or –C(=N-cyano)-;

Y is S(O)$_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, C(O)O-, or S(O)$_n$ wherein n is 0, 1 or 2;

R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen and (C_1-C_6)alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)acylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, cyano, cyano(C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, nitro, nitro(C_1-C_6)alkyl or (C_1-C_6)acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, (C_1-C_6)acyl, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$ amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_1-C_6)alkylamino, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, nitro, cyano(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, nitro(C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)acylamino, (C_1-C_6)acylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, amino(C_1-C_6)acyl(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)acyl, $R^{15}R^{16}$N-CO-O-, $R^{15}R^{16}$N-CO-(C_1-C_6)alkyl, R^{15}C(O)NH, R^{15}OC(O)NH, R^{15}NHC(O)NH, (C_1-C_6)alkyl-S(O)$_m$, (C_1-C_6)alkyl-S(O)$_m$-(C_1-C_6)alkyl, $R^{15}R^{16}$NS(O)$_m$, $R^{15}R^{16}$NS(O)$_m$ (C_1-C_6)alkyl, R^{15}S(O)$_m$ R^{16}N, or R^{15}S(O)$_m$$R^{16}$N($C_1$-$C_6$)alkyl, wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl;

R^{12} is cyano, trifluoromethyl, (C_1-C_6)alkyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_2-C_6)alkynyl, cyano(C_1-C_6)alkyl, (C_1-C_6)alkyl-S(O)$_m$ wherein m is 0, 1 or 2;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and (C_3-C_{10})cycloalkyl, wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6)alkylthio, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_5-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl, (C_3-C_9)cycloalkyl or (C_6-C_{10})aryl; or R^2 and R^3 are each independently (C_3-C_{10})cycloalkyl, (C_3-C_{10})cycloalkoxy, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_6-C_{10})arylamino, (C_1-

C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)acyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyamino-CO-, (C_5-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl or (C_6-C_{10})aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-NH-, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy, carboxy, carboxy(C_1-C_6)alkyl, carboxy(C_1-C_6)alkoxy, benzyloxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_6-C_{10})aryl, amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonylamino, (C_6-C_{10})aryl(C_1-C_6)alkoxycarbonylamino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-NH-, (C_1-C_6)alkyl-CO-NH-, cyano, (C_5-C_9)heterocycloalkyl, amino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-, ((C_1-C_6)alkyl)$_2$amino-CO-NH-, (C_6-C_{10})arylamino-CO-NH-, (C_5-C_9)heteroarylamino-CO-NH-, (C_1-C_6)alkylamino-CO-NH-(C_1-C_6)alkyl, ((C_1-C_6)alkyl)$_2$amino-CO-NH-(C_1-C_6)alkyl, (C_6-C_{10})arylamino-CO-NH-(C_1-C_6)alkyl, (C_5-C_9)heteroarylamino-CO-NH-(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonylamino, (C_6-C_{10})arylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_5-C_9)heteroaryl or (C_2-C_9)heterocycloalkyl.

20. (Amended) A compound according to claim 1, wherein said compound is selected from the group consisting of:

Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

~~({4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl}-amino)-acetic acid ethyl ester;~~

3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;

3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;

1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one; and

1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one~~;~~

~~N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamidine; and~~

~~N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamidine~~.

22. (Amended) A pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, ~~leukemia~~ and ~~other~~ autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional agents which modulate a mammalian immune

system or with antiinflammatory agents, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

26. (Amended) A method for treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, ~~leukemia~~ and ~~other~~ autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, effective in treating such a condition.

27. (New) A pharmaceutical composition of claim 22, wherein the disorder or condition is the cancer leukemia.

28. (New) A pharmaceutical composition of claim 22, wherein said additional agent is cyclosporin A, rapamycin, tacrolimus, leflunomide, deoxyspergualin, mycophenolate, azathioprine, daclizumab, OKT3, AtGam, aspirin, acetaminopehn, ibuprofen, naproxen, piroxicam or an anti-inflammatory steroid.

29. (New) A method of claim 26, wherein the disorder or condition is the cancer leukemia.

30. (New) A method of claim 26, wherein said additional agent is cyclosporin A, rapamycin, tacrolimus, leflunomide, deoxyspergualin, mycophenolate, azathioprine, daclizumab, OKT3, AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam or an anti-inflammatory steroid.

31. (New) A compound of 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, or pharmaceutically acceptable salt thereof.